Section II (Remarks)

Cancellation and Amendment of Claims

Claims 6-7 and 9-13 have been canceled herein, and claims 3, 4, 5, 8, 14, 15 and 16 have been amended. New claims 17-18 have been added, to claim specific ones of the alternative determinations recited in amended claim 16.

Amended claim 16 now recites an *in vitro* method for assessment of a liver tissue sample from a subject, to determine presence of or susceptibility to NASH in said subject, which comprises: a) detecting and quantifying in said liver tissue sample the level of the following proteins: apolipoprotein A1 (APA1), mitochondrial ATPase β subunit (ATPB), leukotriene A4 hydrolase (LKHA), keratin 18 (K1CR), guanidinoacetate N-methyltransferase (GAMT), superoxide dismutase (SODC), albumin (ALBU), antioxidant protein 2 (AOP2) (isoforms 1 and 2), prohibitin 1 (PHB1), methionine adenosyl transferase (MAT), long-chain acyl-CoA dehydrogenase (ACDL), and selenium binding protein (SBP); b) comparing the results obtained in step a) with normal reference values for said proteins in liver tissue; and c) based on said comparing, determining presence of or susceptibility to NASH in said subject.

Thus, the method of amended claim 16 comprises the detection and quantification of all 13 above-mentioned proteins, including the two isoforms of antioxidant protein 2.

Claim 16 as now amended is fully consistent with and supported by the disclosure of the originally filed application, e.g., the disclosure at page 10, lines 31-32 ("it is preferable to detect and quantify the level of two or more of said proteins..."), and original claim 7 ("two or more proteins..."). See also the last sentence of the Abstract of the application ("[B]y comparing the results obtained with the normal values of such proteins in healthy hepatic tissue, the method can be used to diagnose NASH and/or to assess a patient's potential risk of developing NASH").

No new matter (35 USC 132) has been introduced.

Claims 3, 5, and 8 have been amended for consistency with amended claim 16.

Claim 14 has been amended to place same in independent form, in response to the rejection of same under 35 U.S.C. § 112, second paragraph. Claim 14 now recites a method of assessing a subject to identify presence of or susceptibility to NASH, in terms consistent with those of claim 16 as amended, to set out active, positive steps for the claimed methodology.

In addition to the foregoing, claim 4 has been amended to insert a Markush recital so that the antibodies specified therein are identified as "antibodies selected from the group consisting of monoclonal antibodies, polyclonal antibodies . . . ." Such amendment makes clear that the recited varieties of antibodies are species of the selection group, with proper Markush format being specified.

Claim 5 has been amended for grammatical consistency and to replace the phrase "of the kind of" with the term "comprising" in reference to the biochips or protein microarrays.

Claims 1-5, 8 and 14-18 now are pending in the application.

Rejections of the Claims under 35 U.S.C. 112, Second Paragraph, and 35 U.S.C. 101

Claims 1-16 have been rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention, and as being incomplete for omission of essential steps. This rejection is traversed.

Claims 14 and 16 as now amended affirmatively recite steps for carrying out the method to determine whether a subject has or is susceptible to NASH based on comparison of the 13 specified proteins with normal reference values. Since all 13 proteins are utilized in the claimed methodology of the invention, the fact that specific ones of such 13 proteins are markers for other symptoms or disease states is irrelevant to the use of the entire group to indicate the presence of or susceptibility to NASH in a subject.

Further, the Examiner's statement that one of ordinary skill would further need to know levels of the different markers relative to reference values to make the diagnosis and distinguish from

other disease states is acknowledged, and is addressed by the use of all 13 proteins in the claimed methodology of the invention.

In this respect, the Examiner's statement that "applicants appear to require measurement of at least two different markers" (page 3, paragraph 5 of the Office Action) has been addressed in the amended claims of the application, which require use of all 13 specified proteins for diagnosis of presence of or susceptibility to NASH.

Accordingly, the claims as amended herein are submitted to embody essential steps and to properly specify the methodology of applicants' claimed invention.

As indicated above, claim 14 has been amended to specify the particular steps for assessing a subject, by recital of active, positive steps.

Based on the foregoing, the claims are fully in compliance with 35 U.S.C. § 112, second paragraph.

Further, concerning the rejection of claims 14-15 under 35 U.S.C. § 101 as lacking steps involved in the process (page 3, paragraph 9 of the October 16, 2006 Office Action), the above-discussed amendment of claim 14 and amendment of claim 15 consistent with claim 14, obviates such § 101 rejection.

Rejection of Claims Under 35 U.S.C. § 102 and Traversal Thereof

In the October 16, 2006 Office Action, claims 1-7, 9 and 10 have been rejected under 35 U.S.C. § 102(e) as anticipated by Rose *et al.* (U.S. Patent Application Publication No. 2006/0084067). In addition, claims 1-4 were rejected in such Office Action under 35 U.S.C § 102(a) as anticipated by Santamaria *et al.*, Functional proteomics of nonalcoholic steatohepatitis: mitochondrial proteins as targets of S-ademosylmethionine, March 2003, PNAS, 100(6) P.3065-3070.

Such rejections are traversed, and amended.

Patentability of Pending Claims 1-5, 8 and 14-18

Rose *et al.* (U.S. Patent Application Publication No. 2006/0084067) disclose a method of diagnosing the presence or severity of liver fibrosis in an individual, by: detecting α2-macroglobulin (α2-MG), hyaluronic acid (HA) and tissue inhibitor of a metalloproteinases-1 (TIMP-1) in a sample from the individual; and diagnosing the presence or severity of liver fibrosis based on the presence or level of α2-MG, HA and TIMP-1 (Abstract).

The requirement for a proper rejection of claims under 35 U.S.C. § 102 is set out in MPEP § 2131 ("Anticipation - Application of 35 U.S.C. 102(a), (b), and (e)") following the quotation of the statute:

"TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM"

– MPEP §2131

The principle of this boldfaced and capitalized heading then is explained in this MPEP section with reference to the applicable case law:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). ... "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim... *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).
>
> (emphasis added; MPEP §2131)

Rose does not meet the foregoing criteria in application to claims 1-5 as amended herein (it being noted that the additional claims 6-7, 9 and 10 rejected based on Rose have been cancelled herein, so that the rejection on the stated grounds is moot as to such claims).

In relation to claims 1-5, the following distinctions between Rose and the subject matter of applicants' claims are to be noted.

[1] The present invention relates to a method for the diagnosis of presence of or susceptibility to **NASH** while the method disclosed by Rose *et al.* relates to a method of diagnosing **liver fibrosis**. NASH and liver fibrosis are different liver diseases. NASH is a progressive liver disease characterized by accumulation of fatty acids in the hepatocytes, followed by inflammation, and does not necessarily involve fibrosis. In fact, only a minor portion of NASH patients suffer from fibrosis. It also is noted that fibrosis is a liver lesion that is also present in various other diseases that have nothing to do with NASH (e.g., viral hepatitis). In view of such fundamental distinction between NASH and liver fibrosis, a difference that is well-recognized in the field of the invention, the present claimed invention is distinguished from the disclosure of Rose *et al.*

[2] The Examiner's attention in this respect is directed to the following references, as concurrently made of record by an accompanying Information Disclosure Statement:

- Bacon BR (Gastroenterology 1995; 108(5):1607), which states that only 39% of NASH patients presented fibrosis; and

- a review by the American Gastroenterological Association AGA) (Gastroenterology 2002;123:1705-1725) in which it is mentioned that: "The original descriptions of steatohepatitis included the additional presence of Mallory bodies, ballooning degeneration, predominately lobular neutrophilic inflammation, and Rappaport zone III perisinusoidal fibrosis. It is now appreciated that, in a given patient, only some of these features may be present." [emphasis added; page 1705, right column, last paragraph].

[3] The method disclosed by Rose *et al.* is a method of diagnosing the presence or severity of liver fibrosis in an individual by detecting α2-MG, HA and TIMP-1 in a sample from the individual, optionally including the detection of other molecular markers such as APA1 and/or SODC (Rose *et al.*, page 16, paragraphs 0121-0122). However, Rose *et al.* do not disclose or in any way suggest the specific constellation of 13 proteins utilized in the method of the present invention. This fact is consistent with the stated objective of Rose *et al.* being the diagnosis of presence or severity of liver fibrosis, a disease state that is different from and non-analogous to NASH.

Rose *et al.* thus use a different collection of markers than the collection of 13 proteins required by applicants' methodology, and Rose *et al.* is directed to assaying for presence or severity of liver fibrosis, a different and non-equivalent disease state to NASH.

Since Rose *et al.* fail to disclose each and every protein utilized by applicant in their claimed methodology, and since Rose *et al.* is directed to a different disease state than the methodology of applicants' claimed invention, Rose *et al.* cannot anticipate the subject matter of applicants' claims. Further, there is no derivative basis in Rose *et al.* for the methodology of applicants' claimed invention.

It therefore is requested that the rejection of claims 1-5, as presently pending, be withdrawn.

Concerning the rejection of claims 1-4 under 35 U.S.C. § 102(a) as anticipated by Santamaria *et al.*, the Examiner has indicated that the foreign priority must be perfected in order to remove such reference as prior art. In response, enclosed and submitted herewith (Appendix A hereof) is an English translation and accompanying certification of Vicente Gonzalez Diaz, the translator of the document, stating that such English translation "is a true translation to the best of my knowledge and belief."

By such perfection of the priority via submission of the certified English translation, the disclosure of Spanish Patent Application No. P200202911 filed December 18, 2002 is established, to remove the Santamaria *et al.* reference as prior art under § 102(a).

It therefore is requested that the rejection of claims 1-4 as anticipated by Santamaria *et al.* be withdrawn.

[It is noted that the anticipation rejection based on Santamaria has been applied to claims 1-4 in paragraph 18 at page 5 of the October 16, 2006 Office Action, but the subsequent discussion of such reference in paragraphs 19-24 of the Office Action addresses the other claims of the application. It appears that the rejection was intended to be applied to claims 1-14 and 16. By the above-discussed removal of Santamaria *et al.* as a prior art reference under § 102(a), the application of such reference to other claims is likewise overcome.]

Petition for Extension of Time under 37 CFR 1.136 and Payment of Appertaining Extension Fee Specified by 37 CFR 1.17

Petition hereby is made for a three months extension of time, for response to the October 16, 2006 Office Action, extending the deadline from January 16, 2007 to April 16, 2007.

The fee of $510.00 specified in 37 CFR 1.17(a)(3) is enclosed in the form of a Credit Card Authorization Form authorizing charging of such amount to the credit card identified in the Form.

Authorization also is hereby given to charge the amount of any deficiency of fees otherwise due and payable for this response, to Deposit Account No. 08-3284 of Intellectual Property/ Technology Law.

Notice of Claim of Small Entity Status

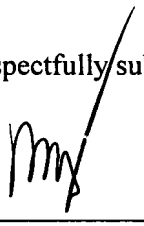
Small entity status under 37 CFR 1.9 is hereby claimed for this application.

CONCLUSION

Claims 1-5, 8 and 14-18 as amended/added are now in form and condition for allowance. Favorable action is requested.

If any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned attorney at (919) 419-9350 to discuss same, in order that the prosecution of the application can be expedited in favor of early allowance of the application.

Respectfully submitted,



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